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APPLICATION NUMBER: 60/461,338

FILING DATE: April 08, 2003

RELATED PCT APPLICATION NUMBER: PCT/US04/07422

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04-10-03 60/461338 1040803/Pre

PTO/SB/16 (10-01)
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

Express Mail Label No. EL 957198821 US

| INVENTOR(S) | | | | |
|---|------------------------|---|--|--|
| Given Name (first and middle [if any]) | Family Name or Surname | Residence (City and either State or Foreign Country) | | |
| Laurence C. Shozo | Chow Takagi | Gaithersburg, MD Gaithersburg, MD | | |
| <input type="checkbox"/> Additional inventors are being named on the _____ separately numbered sheets attached hereto | | | | |
| TITLE OF THE INVENTION (500 characters max) | | | | |
| Premixed Self-Hardening Bone Graft Pastes | | | | |
| CORRESPONDENCE ADDRESS | | | | |
| Direct all correspondence to: | | | | |
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| ENCLOSED APPLICATION PARTS (check all that apply) | | | | |
| <input checked="" type="checkbox"/> Specification Number of Pages | | 8 | <input type="checkbox"/> CD(s), Number | |
| <input type="checkbox"/> Drawing(s) Number of Sheets | | 1 | <input type="checkbox"/> Other (specify) | |
| <input type="checkbox"/> Application Data Sheet. See 37 CFR 1.76 | | | | |
| METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT | | | | |
| <input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. | | | | |
| <input type="checkbox"/> A check or money order is enclosed to cover the filing fees | | | | |
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| The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government. | | | | |
| <input checked="" type="checkbox"/> No. | | | | |
| <input type="checkbox"/> Yes, the name of the U.S. Government agency and the Government contract number are: _____ | | | | |

Respectfully submitted, Rebecca P. Rokos
SIGNATURE

Date 04/08/03

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Docket Number: 10118.00019

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

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By: Rebecca P. Law

Chow, et al, U.S. Provisional Patent Application for "PREMIXED SELF-HARDENING BONE GRAFT PASTES"

- Provisional Transmittal Form (in duplicate)
- Fee Transmittal (in duplicate)
- Provisional Application (8 pages) and 1 sheet of drawings
- Return Receipt Postcard

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PREMIXED SELF-HARDENING BONE GRAFT PASTES

BACKGROUND OF THE INVENTION

- [01] A self-hardening calcium phosphate cement ("CPC"), consisting of tetracalcium phosphate ($\text{Ca}_4(\text{PO}_4)_2\text{O}$, "TTCP") and dicalcium phosphate anhydrous (CaHPO_4 , "DCPA"), has been shown in clinical studies to be efficacious for repairing bone defects. The hardening time of such conventional cements is as long as about 30 minutes with water, although hardening time can be shortened if a phosphate solution is used as the cement liquid. Hydroxyapatite ($\text{Ca}_5(\text{PO}_4)_3\text{OH}$, "HA") is formed as the product. More recently, additional CPCs that contain α -tricalcium phosphate ($\alpha\text{-Ca}_3(\text{PO}_4)_2$, " α -TCP") and CaCO_3 or DCPA and $\text{Ca}(\text{OH})_2$ have also been developed. These cements may harden in about 10 minutes when a phosphate solution is used as the cement liquid. They also form hydroxyapatite as the final product.
- [02] Most conventional CPCs are mixed with an aqueous solution immediately before application. In the clinical situation, the ability of the surgeon to properly mix the cement and then place the cement paste in the defect within the prescribed time is a crucial factor in achieving optimum results.
- [03] A premixed CPC paste containing the TTCP and DCPA powders and glycerol as the cement liquid has been used for root canal filling, sealing, and injectability. The cement paste was found to be stable in a syringe but hardened only after being delivered into the root canal where it became exposed to water from the surrounding tissues. Because the cement paste was injected into a confined area, there was little concern of disintegration of the paste due to washout. Although the premixed CPC was shown to have improved biocompatibility with periapical bone tissue than a number of conventional root canal filling or sealing materials, the premixed CPC-glycerol paste did not exhibit a good washout resistance when it was applied to an open wet field.
- [04] Premixed self-hardening cements have been formulated by mixing glycerol, sodium phosphate (" Na_2HPO_4 "), and hydroxypropyl methyl cellulose ("HMC") with CPC powders. Although HMC and Na_2HPO_4 may serve to improve the paste cohesiveness

and accelerate cement hardening, respectively, the hardening times ("HT") of these cements were greater than 60 minutes.

- [05] There remains a need for premixed cement pastes that are stable in the package, are resistant to washout, and will harden only after being deposited at the site of the defect but, once placed, will then harden within a predetermined time.

DETAILED DESCRIPTION OF THE INVENTION

- [06] Premixed calcium cement pastes for use in bone graft and similar medical repair applications are provided. The pastes may be injectable for delivery to the bone defect site. The pastes can be prepared by mixing CPC powders with non-aqueous, but water miscible, liquids. Non-aqueous liquids are preferred to limit premature hardening of the pastes, which may harden in aqueous environments. Gelling agents, such as HMC, carboxymethyl cellulose ("CMC"), alginate, chitosan, and the like, can be mixed with the powders to enhance washout resistance.
- [07] A number of carboxylic acids form calcium complexes that are not highly soluble. These acids include glycolic, citric, tartaric, malonic, malic, and maleic acids. Some of these acids, when mixed with a powder containing one or more of calcium phosphate compounds produce fast hardening cements. Thus, it is possible that the use of these acids, can produce faster setting premixed cements. Since the hardening in these cements is due to Ca-complex formation, self-hardening cements of these type can also be formulated using Ca-containing compounds instead of or in combination with calcium phosphate compounds.
- [08] For most clinical applications, a hardening time of more than 60 minutes is too long. Premixed CPCs or self-hardening bone graft pastes in accordance with the present invention will have an HT of no more than about 35 minutes, preferably no more than 20 minutes and even more preferably between about 5 to about 15 minutes.
- [09] Bone graft pastes ("BGPs") may include a non-toxic, calcium containing or calcium phosphate-containing powder, a non-toxic organic carboxylic acid capable of forming calcium complexes, and a non-toxic, non-aqueous, water-miscible liquid. The calcium

phosphate powder can include MCPM, MCPA, DCPA, DCPD, OCP, α -TCP, β -TCP, amorphous calcium phosphate, calcium deficient HA, non-stoichiometric HA, TTCP CaSO_4 , $\text{CaSO}_4 \cdot 0.5 \text{H}_2\text{O}$, $\text{CaSO}_4 \cdot 2 \text{H}_2\text{O}$, CaO , $\text{Ca}(\text{OH})_2$, and CaCO_3 and combinations thereof. The Ca/P molar ratio of TTCP is preferably between about 1.67 to about 2, of α -TCP is between about 1.5 to about 1.67, and of β -TCP is between about 1.50 to about 1.67. The particle sizes of the compounds are between about 1 to about 200 μm and more preferably between about 2 to about 50 μm . The organic acid may include glycolic, tartaric, malonic, malic and citric acid and combinations thereof. The non-aqueous, water-miscible liquid may include glycerin, poly(propylene glycol), poly(ethylene glycol), and combinations thereof. The compositions also may include a non-toxic gelling agent to enhance paste cohesiveness and washout resistance. The gelling agent may include HMC, CMC, chitosan, collagen, gum, gelatin, and alginate, and combinations thereof.

EXAMPLES

- [10] The following examples further illustrate preferred embodiments of the present invention but are not be construed as in any way limiting the scope of the present invention as set forth in the appended claims.
- [11] Various premixed self-hardening BGPs were prepared. Hardening times and other properties of the BGPs were evaluated.
- [12] **Preparation of the solid ingredients of premixed BGP:** TTCP was prepared by heating an equimolar mixture of commercially obtained DCPA (Baker Analytical Reagents, J.T. Baker Chemical Co., Phillipsburg, NJ) and CaCO_3 (J.T. Baker Chemical Co.) at 1500°C for 6 hours in a furnace and quenched at room temperature. The powders were ground individually in a planetary ball mill in cyclohexane, ethanol, or without a liquid to obtain the desired median particle sizes based on data from previous studies. The median particle sizes of TTCP and DCPA were 17.1 μm and 1.7 μm , respectively.
- [13] α -TCP was prepared by heating a mixture that contained 2 mol of DCPA and 1 mol of CaCO_3 to 1500°C for 6 hours and then quenched in air. The powders were ground

individually in a planetary ball mill in cyclohexane, ethanol, or without a liquid to obtain the desired median particle sizes based on data from previous studies. The median particle sizes of α -TCP and CaCO_3 were $4.6\ \mu\text{m}$ and $3.9\ \mu\text{m}$, respectively. The median particle size of Ca(OH)_2 was $2.2\ \mu\text{m}$. The particle sizes of the components of BGPs prepared in accordance with the present invention generally can be in the range of 1 to $50\ \mu\text{m}$.

[14] **Liquid ingredients of controls and premixed BGPs:** All ingredients were obtained commercially. A homogeneous mixture of a carboxylic acid, HMC or CMC, and glycerin was produced by blending the mixture in a ball mill.

[15] **Preparation of premixed pastes:** Premixed BGP compositions were prepared by mixing BGP powder and a predetermined liquid at desired powder-to-liquid mass ratios (P/L) on a mixing block until a smooth and homogenous paste was obtained.

[16] Premixed BGP 1

Solid phase: TTCP (73 mass %) and DCPA (27 mass %)

Liquid phase: Glycerin (62.2 mass %), d-tartaric acid (37.5 mass %), and HMC (0.3 mass %)

P/L: 3.0

[17] Premixed BGP-2

Solid phase: TTCP (73 mass %) and DCPA (27 mass %)

Liquid phase: Glycerin (62.2 mass %), glycolic acid (37.5 mass %), and HMC (0.3 mass %)

P/L: 3.0

[18] Premixed BGP 3

Solid phase: TTCP (73 mass %) and DCPA (27 mass %)

Liquid phase: Glycerin (70.5 mass %), malonic acid (29 mass %), and HMC (0.5 mass %)

P/L: 3.0

Hardening time: 15 ± 1 (min mean \pm s.d.; n = 3)

[19] Premixed BGP 4

Solid phase: TTCP (73 mass %) and DCPA (27 mass %)

Liquid phase: Glycerin (79.5 mass %), maleic acid (20 mass %), and HMC (0.5 mass %)

P/L: 3.0

[20] Premixed BGP 5

Solid phase: TTCP (73 mass %) and DCPA (27 mass %)

Liquid phase: Glycerin (49.3 mass %), citric acid (49.2 mass %), and CMC (1.5 mass %)

P/L: 2.3

[21] Premixed BGP 6

Solid phase: TTCP (39.1 mass %) and α -TCP (60.9 mass %)

Liquid phase: Glycerin (61.9 mass %), d-tartaric acid (37.1 mass %), and CMC (1 mass %)

P/L: 1.5

No indentation after 15 minutes.

[22] Premixed BGP 7

Solid phase: TTCP (55 mass %), DCPA (20 mass %), α -TCP (25 mass %)

Liquid phase: Glycerin (61.9 mass %), d-tartaric acid (37.1 mass %), and CMC (1 mass %)

P/L: 1.5

[23] Premixed BGP 8

Solid phase: TTCP

Liquid phase: Glycerin (61.9 mass %), d-tartaric acid (37.1 mass %) and CMC (1 mass %)

P/L: 1.5

[24] Premixed BGP 9

Solid phase: α -TCP

Liquid phase: Glycerin (61.9 mass %), d-tartaric acid (37.1 mass %), and CMC (1 mass %)

P/L: 1.5

[25] **Washout resistance test:** The washout resistance of the premixed BGPs was tested as follows. Premixed BGP samples were shaped into a small sphere by hand, and then placed immediately in a 5 mL of physiologic-like solution ("PLS") (1.15 mM Ca, 1.2 mM P, 133 mM NaCl, 50 mM HEPES, pH = 7.4) at 37 °C. The sample was considered to pass the washout resistance test if it did not visibly disintegrate in the PLS.

[26] **Diametral tensile strength ("DTS") measurement:** DTS samples were prepared by placing the premixed paste into a mold (6 mm diameter by 3 mm height) with about 2 MPa of applied pressure. The mold was covered with two fritted glass slides (pore size of about 40 μ m to about 60 μ m, thickness of about 3.5 mm) and immersed in PLS at 37 °C. Glycerol-PLS exchange occurred through the fritted glass, allowing the BGP to harden (Fig. 1). Samples were removed from molds at about 4 hours, and then each sample was immersed in 30 mL of PLS for an additional 20 hours. In some cases, additional samples

were prepared and samples were immersed in PLS for an additional 6 days with the PLS being changed daily (30 mL/specimen at 37 °C) to investigate the effect of PLS immersion on physicochemical properties. DTS values (standard uncertainty equals 5 %) were measured on a Universal Testing Machine (United Calibration Corp, Garden Grove, CA) using a loading rate of 10 mm/min,

- [27] **Hardening time measurements:** The Gilmore needle method (standard uncertainty equals 5 %) was used to measure hardening time on samples prepared as described above for DTS measurements.
- [28] **Assessments of hydroxyapatite formation:** Powder X-ray diffraction ("XRD") analysis was used to estimate the extent of BGP conversion to HA. The estimated standard uncertainty in 20 measurements is 0.01° and the minimum mass fraction of a calcium phosphate phase that can be detected by XRD is about 3 %.

[29] **Hardening time (HT) Results**

Premixed Paste HT (min, n = 3)

| | |
|------|--------|
| BGP1 | 10 ± 1 |
| BGP2 | 15 ± 1 |
| BGP3 | 20 ± 1 |
| BGP4 | 20 ± 1 |
| BGP5 | 35 ± 1 |
| BGP6 | 15 ± 1 |
| BGP7 | 25 ± 1 |
| BGP8 | 35 ± 1 |
| BGP9 | 20 ± 1 |

[30] **Diametral Tensile (DTS) Strength**

DTS of some of the premixed BGP samples were determined as given below.

| Premixed paste | 1-day DTS (MPa) | 7-day DTS (MPa) |
|----------------|------------------|-----------------|
| BGP1 | 4.3 ± 0.3 (n =5) | 3.8 ± 0.3 |
| BGP2 | 3.1 ± 0.5 | 3.0 ± 0.3 |
| BGP3 | 2.3 ± 0.4 | 2.7 ± 0.3 |

- [31] **Hydroxyapatite ("HA") Formation:** Complete and near complete conversion of the initial cement ingredients to HA was found in all 7-day samples of premixed BGPs. As an example, Figure 1 illustrates the XRD pattern of 7-day samples of premixed BGP 1, showing a low crystalline hydroxyapatite as the product.
- [32] While particular embodiments of the present invention have been described and illustrated, it should be understood that the invention is not limited thereto as modifications may be made by persons skilled in the art. The present application contemplates any and all modifications that fall within the spirit and scope of the underlying invention disclosed herein.

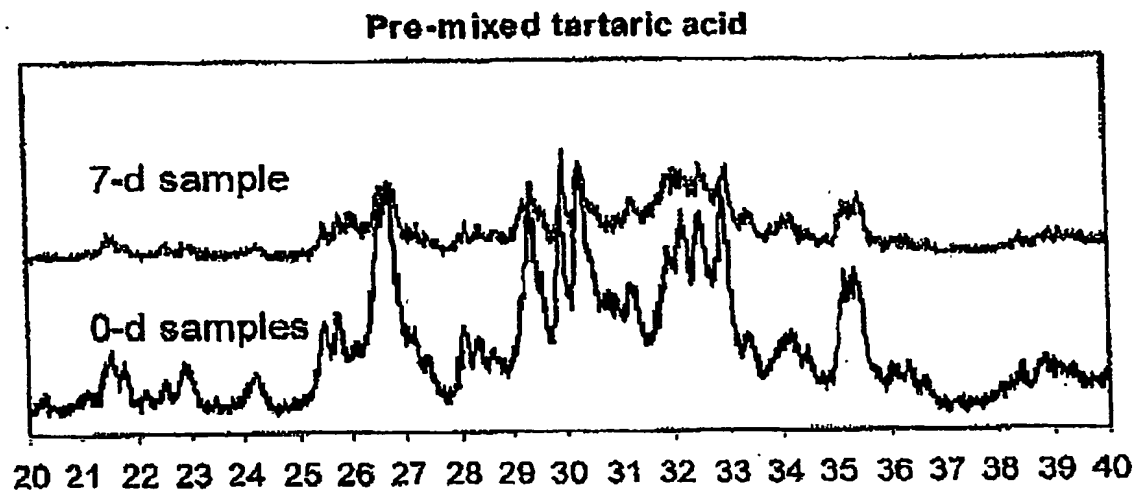


FIGURE 1

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